CYCLIZATION OF SUBSTITUTED PHENYL *N*-(2-HYDROXYBENZYL)CARBAMATES IN APROTIC SOLVENTS. SYNTHESIS OF 4*H*-1,3-BENZOXAZIN-2(3*H*)-ONES

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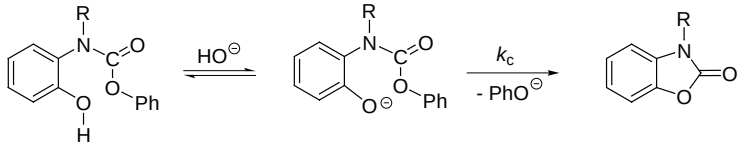
The kinetics of cyclization of substituted phenyl *N*-(2-hydroxybenzyl)carbamates and their *N*-methyl analogs, prepared by the reaction of 2-(aminomethyl)phenols with substituted phenyl chloroformates, was studied in dioxane or toluene at the temperatures 110–180 °C. Electron-withdrawing substituents in the leaving phenoxy group strongly accelerate the rate of cyclization ($\rho = 2.45 \pm 0.15$) while the substituents in the other ring have virtually no effect. The cyclization was catalyzed with triethylamine in toluene but not in dioxane. On the basis of these results, the most convenient method for preparation of substituted 4*H*-1,3-benzoxazin-2(3*H*)-ones was a one-hour reflux of substituted 4-nitrophenyl *N*-(2-hydroxybenzyl)carbamates in dioxane. Based on the influence of substituents, solvents (dioxane and toluene) and triethylamine, the reaction mechanism and structure of the transition state were proposed.

Key words: Carbamates; Cyclizations; Kinetics; Benzoxazines; Benzoxazinones; Substituent effects.

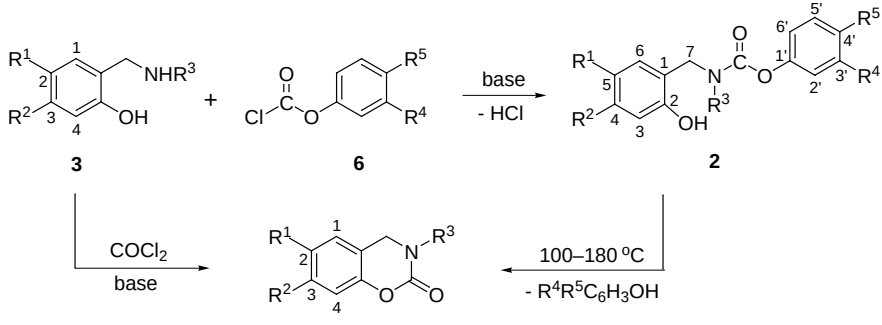
4*H*-1,3-Benzoxazin-2(3*H*)-ones **1** and aryl *N*-benzylcarbamates **2** inhibit the activity of acetylcholinesterase[1] and hence are biologically active compounds. Benzoxazin-2-ones are phoshodiesterase inhibitors and antithrombotic pharmaceuticals[2]. The syntheses of 4*H*-1,3-benzoxazin-2(3*H*)-ones **1** published so far use 2-(aminomethyl)phenols **3** cyclized with phosgene in the presence of *N*,*N*-dimethylaniline[3]. A thermal cyclization of (2-hydroxyphenyl)acetylazide to 4*H*-1,3-benzoxazin-2(3*H*)-one in benzene solution was also described[4]. The intramolecular reactions of similar compounds in water at 25 °C catalyzed by hydroxide ion (Scheme 1) was published[5,6]. The rate constant of aryl *N*-(2-hydroxyphenyl)carbamates **4** is *ca* ten times lower than that of *N*-methyl-*N*-(2-hydroxyphenyl)carbamates **5**. The autors[5] estimated that the cyclization of **4** is *ca* 8 order of magnitudes faster the the intermolecular reaction of *N*-(4-hydroxyphenyl)carbamates.



5, R = CH_3
4, R = H

SCHEME 1

The aim of this work was to study a new two-step non-phosgene synthesis of 4*H*-1,3-benzoxazin-2(3*H*)-ones **1a**–**1g** by cyclization of substituted phenyl *N*-(2-hydroxybenzyl)carbamates **2a**–**2o**, prepared by reaction of 2-(aminomethyl)phenols **3a**–**3g** with substituted phenyl chloroformates **6a**–**6e** (Scheme 2) and the kinetics of cyclization and determination of reaction mechanism. The yields of oxazines **1a**–**1g** prepared by this method are compared with the one-step phosgenation method.



3 **6** **2**

1

	R^1	R^2	R^3		R^4	R^5		R^1	R^2	R^3	R^4	R^5		R^1	R^2	R^3	R^4	R^5		R^1	R^2	R^3
3a	H	H	H	**6a**	H	H	**2a**	H	H	H	H	H	**2i**	H	H	Me	NO_2	H	**1a**	H	H	H
3b	H	H	Me	**6b**	Cl	H	**2b**	H	H	H	Cl	H	**2j**	H	H	Me	H	NO_2	**1b**	H	H	Me
3c	Br	H	Me	**6c**	H	Cl	**2c**	H	H	H	H	Cl	**2k**	Br	H	Me	H	NO_2	**1c**	Br	H	Me
3d	H	Cl	Me	**6d**	NO_2	H	**2d**	H	H	H	NO_2	H	**2l**	H	Cl	Me	H	NO_2	**1d**	NO_2	H	Me
3e	NO_2	H	Me	**6e**	H	NO_2	**2e**	H	H	H	H	NO_2	**2m**	H	NO_2	Me	H	NO_2	**1e**	H	Cl	Me
3f	H	NO_2	Me				**2f**	H	H	Me	H	H	**2n**	NO_2	H	Me	H	NO_2	**1f**	H	NO_2	Me
3g	H	H	Ph				**2g**	H	H	Me	Cl	H	**2o**	H	H	Ph	H	NO_2	**1g**	H	H	Ph
							2h	H	H	Me	H	Cl										

SCHEME 2

EXPERIMENTAL

Melting points were measured on a Koffler instrument and are not corrected. ^{1}H (360 MHz) and ^{13}C (90.56 MHz) NMR spectra were recorded using a Bruker AMX 360 spectrometer as saturated solutions in $CDCl_3$. The ^{13}C NMR chemical shifts were referenced to the solvent

signal and this was recalculated in the δ-scale (δ(^{13}C) 77.00 ppm). The δ(^{1}H) chemical shifts were referenced to the internal hexamethyldisiloxane (δ 0.05 ppm) standard. Coupling constants ^{3}J(H,H) are given in Hz. UV spectra were measured on a Specord M40, Carl Zeiss Jena apparatus; λ are given in nm.

Syntheses

Synthesis of Phenyl *N*-(2-Hydroxybenzyl)carbamates (**2**). General Procedure

A phenyl chloroformate **6** (5 mmol) in diethyl ether (3 ml) was added to a 2-(aminomethyl)phenol **3** (5 mmol) and triethylamine (6 mmol) in diethyl ether (3 ml) and the reaction was monitored by TLC. After stirring at room temperature for 30 min and subsequently saturating the reaction mixture with gaseous hydrogen chloride, the precipitated triethylamine hydrochloride was filtered off. Diethyl ether was distilled off and the crude product was crystallized from a mixture heptane–propan-2-ol (4 : 1).

Phenyl N-(2-hydroxybenzyl)carbamate (**2a**). From **3a** and **6a**. Yield 61%, m.p. 78–80 °C. For $C_{14}H_{13}NO_3$ (243.3) calculated: 69.12% C, 5.44% H, 5.80% N; found: 69.40% C, 5.67% H, 5.86% N. ^{1}H NMR ($CDCl_3$): 7.95 b, 1 H (OH); 7.33 t, 2 H, *J* = 7.9 (H-3′,5′); 7.20 m (overlap), 1 H (H-4); 7.19 t (overlap), 1 H (H-4′); 7.13 d, 1 H, *J* = 8.0 (H-6); 7.08 d, 2 H, *J* = 7.4 (H-2′,6′); 6.90 d, 1 H, *J* = 8.0 (H-3); 6.86 t, 1 H, *J* = 7.4 (H-5); 5.79 b, 1 H (NH); 4.35 d, 2 H, *J* = 6.5 (H-7). UV (MeOH), λ_{max} (log ε): 203 (4.34), 274 (3.41).

3-Chlorophenyl N-(2-hydroxybenzyl)carbamate (**2b**). From **3a** and **6b**. Yield 68%, m.p. 98–99 °C. For $C_{14}H_{12}ClNO_3$ (277.7) calculated: 60.58% C, 4.36% H, 5.02% N; found: 60.49% C, 4.41% H, 5.05% N. ^{1}H NMR ($CDCl_3$): 7.62 b, 1 H (OH); 7.26 t, *J* = 8.0 (H-5′); 7.21 m (overlap), 1 H (H-4); 7.18 m, 1 H (H-4′); 7.14 d (overlap), 1 H (H-6); 7.13 t, 1 H, ^{4}J = 2.0 (H-2′); 7.00 m, 1 H (H-6′); 6.90 d, 1 H, *J* = 8.1 (H-3); 6.87 t, 1 H, *J* = 7.4 (H-5); 5.79 b, 1 H (NH); 4.37 d, 2 H, *J* = 6.5 (H-7). UV (MeOH), λ_{max} (log ε): 203 (4.66), 274 (3.44).

4-Chlorophenyl N-(2-hydroxybenzyl)carbamate (**2c**). From **3a** and **6c**. Yield 69%, m.p. 125–127 °C. For $C_{14}H_{12}ClNO_3$ (277.7) calculated: 60.58% C, 4.36% H, 5.02% N; found: 60.79% C, 4.42% H, 5.31% N. ^{1}H NMR ($CDCl_3$): 7.69 b, 1 H (OH); 7.28 AA′XX′-system, 2 H (H-3′,5′); 7.21 t, 1 H, *J* = 7.8 (H-4); 7.14 d, 1 H, *J* = 7.5 (H-6); 7.03 AA′XX′-system, 2 H (H-2′,6′); 6.90 d, 1 H, *J* = 8.1 (H-3); 6.86 t, 1 H, *J* = 7.5 (H-5); 5.78 b, 1 H (NH); 4.37 d, 2 H, *J* = 6.6 (H-7). UV (MeOH), λ_{max} (log ε): 202 (4.38), 219 (4.27), 274 (3.48).

3-Nitrophenyl N-(2-hydroxybenzyl)carbamate (**2d**). From **3a** and **6d**. Yield 72%, m.p. 113 °C (dec.). For $C_{14}H_{12}N_2O_5$ (288.3) calculated: 58.29% C, 4.16% H, 9.72% N; found: 58.47% C, 4.22% H, 9.51% N. ^{1}H NMR ($CDCl_3$): 8.30 b, 1 H (OH); 8.10 m, 1 H (H-4′); 8.00 t, 1 H, ^{4}J = 2.2 (H-2′); 7.52 t, 1 H, *J* = 7.9 (H-5′); 7.48 m, 1 H (H-6′); 7.22 t, 1 H, *J* = 7.6 (H-4); 7.18 d, 1 H, *J* = 7.1 (H-6); 6.90 d, 1 H, *J* = 7.6 (H-3); 6.89 t, 1 H, *J* = 7.6 (H-5); 5.87 b, 1 H (NH); 4.42 d, 2 H, *J* = 6.5 (H-7). UV (MeOH), λ_{max} (log ε): 202 (4.34), 265 (3.84).

4-Nitrophenyl N-(2-hydroxybenzyl)carbamate (**2e**). From **3a** and **6e**. Yield 75%, m.p. 75 °C (dec.). For $C_{14}H_{12}N_2O_5$ (288.3) calculated: 58.29% C, 4.16% H, 9.72% N; found: 58.22% C, 4,31% H, 9.51% N. ^{1}H NMR ($CDCl_3$): 8.25 b, 1 H (OH); 8.22 AA′XX′-system, 2 H (H-3′,5′); 7.29 AA′XX′-system, 2 H (H-2′,6′); 7.25 (overlap), 1 H (H-4); 7.18 d, 1 H, *J* = 7.0 (H-6); 6.92 d, 1 H, *J* = 8.0 (H-3); 8.89 t, 1 H, *J* = 7.5 (H-5); 5.89 b, 1 H (NH); 4.42 d, 2 H, *J* = 6.4 (H-7). UV (MeOH), λ_{max} (log ε): 203 (4.40), 214 (4.18), 276 (4.08).

Phenyl N-(2-hydroxybenzyl)-N-methylcarbamate (**2f**). From **3b** and **6a**. Yield 73%, m.p. 145–147 °C. For $C_{15}H_{15}NO_3$ (257.2) calculated: 70.06% C, 5.86% H, 5.42% N; found: 70.32% C,

6.04% H, 5.56% N. ^{1}H NMR ($CDCl_3$): 8.65 b, 1 H (OH); 7.36 t, 2 H, *J* = 7.6 (H-3′,5′); 7.26 t, 1 H, *J* = 7.6 (H-4′); 7.22 m, 1 H (H-4); 7.15 d, 1 H, *J* = 7.8 (H-6); 7.09 d, 2 H, *J* = 7.6 (H-2′,6′); 6.96 d, 1 H, *J* = 8.0 (H-3); 6.85 t, 1 H, *J* = 7.5 (H-5); 4.34 s, 2 H (H-7); 3.13 s, 3 H (NCH_3). UV (MeOH), λ_{max} (log ε): 204 (4.34), 275 (3.41).

3-Chlorophenyl N-(2-hydroxybenzyl)-N-methylcarbamate (**2g**). From **3b** and **6b**. Yield 57%, m.p. 120.5–122.0 °C. For $C_{15}H_{14}ClNO_3$ (291.7) calculated: 61.77% C, 4.83% H, 4.82% N; found: 62.04% C, 4. 75% H, 4.64% N. ^{1}H NMR ($CDCl_3$): 8.47 b, 1 H (OH); 7.28 t, *J* = 8.0 (H-5′); 7.22 m (overlap), 1 H (H-4); 7.19 m, 1 H (H-4′); 7.15 d (overlap), 1 H (H-6); 7.12 t, 1 H, ^{4}*J* = 1.8 (H-2′); 6.99 m, 1 H (H-6′); 6.92 d, 1 H, *J* = 8.0 (H-3); 4.40 s, 2 H (H-7), 3.07 s, 3 H (NCH_3). UV (MeOH), λ_{max} (log ε): 204 (4.50), 275 (3.42).

4-Chlorophenyl N-(2-hydroxybenzyl)-N-methylcarbamate (**2h**). From **3b** and **6c**. Yield 47%, m.p. 130.5–133.0 °C. For $C_{15}H_{14}ClNO_3$ (291.7) calculated: 61.77% C, 4.83% H, 4.82% N; found: 61.90% C, 4. 99% H, 4.74% N. ^{1}H NMR ($CDCl_3$): 8.50 b, 1 H (OH); 7.31 AA′XX′-system, 2 H (H-3′,5′); 7.25 t, *J* = 7.5 (H-4); 7.15 d, 1 H, *J* = 7.5 (H-6); 7.04 AA′XX′-system, 2 H (H-2′,6′); 6.95 d, *J* = 7.7 (H-3); 6.85 t, 1 H, *J* = 7.4 (H-5); 4.42 s, 2 H (H-7); 3.12 s, 3 H (NCH_3). UV (MeOH), λ_{max} (log ε): 203 (4.43), 219 (4.30), 275 (3.49).

3-Nitrophenyl N-(2-hydroxybenzyl)-N-methylcarbamate (**2i**). From **3b** and **6d**. Yield 84%, m.p. 110 °C (dec.). For $C_{15}H_{14}N_2O_5$ (302.3) calculated: 59.59% C, 4.73% H, 9.33% N; found: 59.29% C, 4.53% H, 9.24% N. ^{1}H NMR ($CDCl_3$): 8.23 b, 1 H (OH); 8.09 d, 1 H, *J* = 7.4 (H-4′); 8.00 t, 1 H (H-2′); 7.54 t, 1 H, *J* = 7.8 (H-5′); 7.50 d, 1 H, *J* = 7.5 (H-6′); 7.26 t, 1 H, *J* = 7.4 (H-4); 7.17 d, 1 H, *J* = 7.0 (H-6); 6.96 d, 1 H, *J* = 7.7 (H-3); 6.85 t, *J* = 7.4 (H-5); 4.46 s, 2 H (H-7); 3.16 s, 3 H (NCH_3). UV (MeOH), λ_{max} (log ε): 203 (4.40), 265 (3.86).

4-Nitrophenyl N-(2-hydroxybenzyl)-N-methylcarbamate (**2j**). From **3b** and **6e**. Yield 75%, m.p. 121 °C (dec.). For $C_{15}H_{14}N_2O_5$ (302.3) calculated: 59.59% C, 4.73% H, 9.33% N; found: 59.31% C, 4.67% H, 9.28% N. ^{1}H NMR ($CDCl_3$): 8.24 AA′XX′-system, 2 H (H-3′,5′); 8.23 b, 1 H (OH); 7.28 AA′XX′-system, 2 H (H-2′,6′); 7.26 (overlap), 1 H (H-4); 7.16 d, 1 H, *J* = 7.3 (H-6); 6.96 d, 1 H, *J* = 8.0 (H-3); 6.78 t, 1 H, *J* = 7.4 (H-5); 4.46 s, 2 H (H-7); 3.15 s, 3 H (NCH_3). UV (MeOH), λ_{max} (log ε): 204 (4.41), 214 (4.23), 277 (4.08).

4-Nitrophenyl N-(5-bromo-2-hydroxybenzyl)-N-methylcarbamate (**2k**). From **3c** and **6e**. Yield 78%, m.p. 78 °C. (dec.). For $C_{15}H_{13}BrN_2O_5$ (381.2) calculated: 47.26% C, 3.42% H, 7.43% N; found: 47.38% C, 3.32% H, 7.24% N. ^{1}H NMR ($CDCl_3$): 8.30 b, 1 H (OH); 8.24 AA′XX′-system, 2 H (H-3′,5′); 7.32 dd, 1 H, ^{4}*J* = 2.1 (H-4); 7.30 AA′XX′-system, 2 H (H-2′,6′); 7.28 d, 1 H, *J* = 7.5 (H-6); 6.83 d, 1 H, *J* = 8.7 (H-3); 4.40 s, 2 H (H-7); 3.17 s, 3 H (NCH_3). UV (MeOH), λ_{max} (log ε): 204 (4.41), 219 (4.34), 275 (4.05).

4-Nitrophenyl N-(2-hydroxy-4-chlorobenzyl)-N-methylcarbamate (**2l**). From **3d**·HCl and **6e** in the presence of double molar excess of triethylamine. Yield 43%, m.p. 131 °C (dec.). For $C_{15}H_{13}ClN_2O_5$ (336.1) calculated: 53.56% C, 3.87% H, 8.33% N; found: 53.39% C, 4.06% H, 8.30% N. ^{1}H NMR ($CDCl_3$): 8.40 b, 1 H (OH); 8.24 AA´XX´system, 2 H (H-3′,5′); 7.29 AA′XX′-system, 2 H (H-2′,6′); 7.08 d, 1 H, *J* = 7.9 (H-6); 6.95 m, 1 H (H-3); 6.85 t, 1 H (H-5); 4.41 s, 2 H (H-7); 3.14 s, 3 H (NCH_3). ^{13}C NMR ($CDCl_3$): 156.45, 155.72, 155.40, 145.16, 135.74, 131.90, 126.09, 125.09, 122.15, 119.97, 49.54, 34.41. UV (MeOH), λ_{max} (log ε): 204 (4.67), 279 (3.67).

4-Nitrophenyl N-(2-hydroxy-4-nitrobenzyl)-N-methylcarbamate (**2m**). From **3f**·HCl and **6e** in the presence of double molar excess of triethylamine. Yield 86%, m.p. 137 °C. (dec.). For $C_{15}H_{13}N_3O_7$ (347.3) calculated: 51.92% C, 3.82% H, 12.09% N; found: 51.88% C, 3.71% H, 12.33% N. ^{1}H NMR ($CDCl_3$): 8.88 b, 1 H (OH); 8.26 AA′XX′-system, 2 H (H-3′,5′); 7.78 m,

1 H (H-3); 7.73 d, 1 H, *J* = 8.4 (H-5); 7.31 AA′XX′-system, 2 H (H-2′,6′); 7.30 (overlap), 1 H (H-6); 4.53 s, 2 H (H-7); 3.19 s, 3 H (NCH_3). UV (MeOH), λ_{max} (log ε): 203 (4.69), 283 (4.34).

4-Nitrophenyl N-(2-hydroxy-5-nitrobenzyl)-N-methylcarbamate (**2n**). From **3e** and **6e**. Yield 59%, m.p. 151 °C. (dec.). For $C_{15}H_{13}N_3O_7$ (347.3) calculated: 51.92% C, 3.82% H, 12.09% N; found: 51.76% C, 3.64% H, 12.17% N. ^{1}H NMR ($CDCl_3$): 9.48 b, 1 H (OH); 8.26 AA′XX′-system, 2 H (H-3′,5′); 8.17 dd, 1 H, ^4J = 2.7 (H-4); 8.13 d, 1 H (H-6); 7.32 AA′XX′-system, 2 H (H-2′,6′); 7.02 d, 1 H, *J* = 8.9 (H-3); 4.50 s, 2 H (H-7); 3.22 s, 3 H (NCH_3). UV (MeOH), λ_{max} (log ε): 203 (4.38), 283 (4.15).

4-Nitrophenyl N-(2-hydroxybenzyl)-N-phenylcarbamate (**2o**). From **3g** and **6e**. Yield 86%, m.p. 115 °C. (dec.). For $C_{20}H_{16}N_2O_5$ (364.3) calculated: 65.93% C, 4.43% H, 7.69% N; found: 66.21% C, 4.37% H, 7.96% N. ^{1}H NMR ($CDCl_3$): 8.33 b, 1 H (OH); 8.16 AA′XX′-system, 2 H (H-3′,5′); 7.30 m, 2 H (H-3,5-NPh); 7.26 m, 1 H (H-4); 7.20 AA′XX′-system, 2 H (H-2′,6′); 7.17 (overlap), 1 H (H-4-NPh); 7.15 m, 2 H (H-2,6-NPh); 6.96 d, 1 H, *J* = 8.00 (H-6); 6.70 (overlap), 1 H (H-3); 6.70 (overlap), 1 H (H-5); 4.82 s, 2 H (H-7). ^{13}C NMR ($CDCl_3$): 158.24, 155.46, 152.03, 145.01, 139.91, 131.58, 130.27, 129.43, 128.21, 127.39, 124.88, 121.94, 121.49, 119.83, 51.69. UV (MeOH), λ_{max} (log ε): 203 (4.54), 276 (4.08).

Synthesis of Substituted 4*H*-1,3-Benzoxazin-2(3*H*)-ones (**1**). General Procedures

Procedure A. A solution of 5 mmol of 4-nitrophenyl carbamate **2e**, **2j**–**2o** in dioxane (5 ml) was heated under reflux for one hour. After cooling dichloromethane (20 ml) was added and the mixture was extracted several times with 8% aqueous solution of ammonium carbonate until the aqueous phase contained no yellow 4-nitrophenolate. Then the organic phase was washed with water and dried with anhydrous sodium sulfate. The solvent was evaporated and the residue was crystallized from toluene.

4H-1,3-Benzoxazin-2(3H)-one (**1a**). From **2e**. Yield 81%, m.p. 190–192 °C; ref.[7] m.p. 193 °C. UV (MeOH), λ_{max} (log ε): 203 (4.11), 268 (2.91). The formation of **1a** from carbamates **2a**–**2d** in 1 M dioxane solution was verified by HPLC following the reaction carried out at a higher temperature (°C) for the given time (h) with a yield (%): **2a**, 180, 7, 93; **2b**, 150, 7, 95; **2c**, 170, 5, 94; **2d**, 130, 1, 98.

3-Methyl-4H-1,3-benzoxazin-2(3H)-one (**1b**). From **2j**. Yield 80%, m.p. 106–108 °C; ref.[3] m.p. 106–108 °C. ^{13}C NMR ($CDCl_3$): 150.75, 149.79, 127.20, 125.23, 124.07, 116.99, 116,19, 49.38, 36.66. UV (MeOH), λ_{max} (log ε): 203 (4.08), 268 (2.95), 275 (2.89). The formation of **1b** from carbamates **2f**–**2i** in 1 M dioxane solution was verified by HPLC following the reaction carried out at a higher temperature (°C) for the given time (h) with a yield (%): **2f**, 180, 4, 94; **2g**, 150, 4, 95; **2h**, 170, 5, 94; **2i**, 120, 8, 97.

6-Bromo-3-methyl-4H-1,3-benzoxazin-2(3H)-one (**1c**). From **2k**. Yield 77%, m.p. 148.5–151 °C. For $C_9H_8BrNO_2$ (242.1) calculated: 44.72% C, 3.28% H, 5.81% N; found: 44.84% C, 3.56% H, 5.66% N. ^{1}H NMR ($CDCl_3$): 7.32 dd, 1 H, ^3J = 8.00, ^4J = 2.1 (H-3); 7.20 d, 1 H, *J* = 8.0 (H-4); 7.00 d, 1 H, ^4J = 2.3 (H-1); 4.35 s, 2 H (CH_2); 3.12 s, 3 H (NCH_3). ^{13}C NMR ($CDCl_3$): 149.80, 148.61, 131.58, 127.86, 118.83, 116.16, 48.61, 36.14. UV (MeOH), λ_{max} (log ε): 203 (4.32), 230 (3.87), 278 (3.04).

3-Methyl-6-nitro-4H-1,3-benzoxazin-2(3H)-one (**1d**). From **2n**. Yield 85%, m.p. 203–204 °C; ref.[3] m.p. 202.0–204.5 °C. UV (MeOH), λ_{max} (log ε): 202 (4.11), 284 (3.57).

7-Chloro-3-methyl-4H-1,3-benzoxazin-2(3H)-one (**1e**). From **2l**. Yield 64%, m.p. 99.0–101.5 °C. For $C_9H_8ClNO_2$ (197.2) calculated: 54.77% C, 4.06% H, 7.01% N; found: 54.83% C, 3.86% H, 6.86% N. ^{1}H NMR ($CDCl_3$): 7.07 dd, 1 H, ^3J = 8.1, ^4J = 1.6 (H-2); 7.02 d,

1 H, ^4J = 2.1 (H-1); 7.01 d, 1 H, J = 8.1 (H-4); 4.43 s, 2 H (CH_2); 3.11 s, 3 H (NCH_3). UV (MeOH), λ_{max} (log ε): 206 (4.25), 276 (3.06), 282 (3.05).

3-Methyl-7-nitro-4H-1,3-benzoxazin-2(3H)-one (**1f**). From **2m**. Yield 72%, m.p. 157.5–159.0 °C. For $C_9H_8N_2O_4$ (208.1) calculated: 51.90% C, 3.84% H, 6.72% N; found: 52.04% C, 3.66% H, 6.61% N. ^{1}H NMR ($CDCl_3$): 7.23 d, 1 H, J = 8.5 (H-2); 8.13 dd, 1 H, ^4J = 1.8 (H-1); 7.07 d, 1 H, J = 8.9 (H-4); 4.51 s, 2 H (CH_2); 3.17 s, 3 H (NCH_3). UV (MeOH), λ_{max} (log ε): 204 (4.21), 284 (3.35).

3-Phenyl-4H-1,3-benzoxazin-2(3H)-one (**1g**). From **2o**. Yield 81%, m.p. 144–145 °C (2-propanol); ref.[8] m.p. 146 °C.

Procedure B. A solution of substituted 2-(aminomethyl)phenol **2** (5 mmol) and dimethylaniline (10 mmol) in a mixture of toluene (2 ml) and dichloromethane (2 ml) was added dropwise to a solution of phosgene (7 mmol) in toluene (10 ml) with stirring at 0– 10 °C. The mixture was then refluxed for 30 min. After cooling it was washed with 5% solution of hydrochloric acid and then with water. The organic phase was dried, evaporated and the crude product crystallized from ethanol–toluene mixtures. Oxazine yields: **1a** from **3a** (74%); **1b** from **3b** (71%); **1c** from **3c** (69%); **1d** from **3e** (59%); **1g** from **3g** (69%).

Procedure C. To a solution of 2-(aminomethyl)phenol **3a** (5 mmol) and trimethylamine (5 mmol) in dioxane (5 ml) was added dropwise with stirring 4-nitrophenyl chloroformate **6e** (5 mmol) in dioxane (5 ml) at room temperature during 2 min. After another 5 min triethylamine hydrochloride was filtered off and washed with dioxane (5 ml). The dioxane solution was heated to reflux for 1 h. Dioxane was evaporated under reduced pressure and solid residue was dissolved in dichloromethane (15 ml). 4-Nitrophenol was extracted with 8% aqueous ammonium carbonate. After evaporation of dichloromethane 4*H*-1,3-benzoxazin-2(3*H*)-ones **1a** was crystallized from toluene. Yield 93%, m.p. 190–192 °C.

4-Chloro-2-hydroxy-*N*-methylbenzylamine Hydrochloride (**3d**·HCl)

From 4-chloro-2-hydroxybenzaldehyde[9] (7.80 g, 50 mmol) by treatment of methylamine (16 ml of 10% methanolic solution, 50 mmol) for 20 min at room temperature. The solution of imine was mixed with sodium borohydride (0.57 g, 55 mmol) at room temperature. After 30 min the mixture was acidified with 5% aqueous hydrochloric acid to pH 1. After that the solution was alkalized with 5% aqueous sodium hydroxide to pH 10. The organic phase was extracted three times with 30 ml of ether. The separated organic phase was washed three times with water and dried with anhydrous sodium sulfate. Gaseous hydrogen chloride was bubbled into the solution cooled to 10 °C for 2 min. The separated product was filtered off and washed with ether. Yield 3.0 g (36%), m.p. 191.0 °C (dec.). ^{1}H NMR (D_2O): 6.99 d, 1 H, J = 8.1 (H-6); 6.70 d, 1 H, J = 1.9 (H-3); 6.68 dd, 1 H, ^3J = 8.1, ^4J = 1.9 (H-5); 3.88 s, 2 H (CH_2); 2.44 s, 3 H (CH_3).

2-Hydroxy-*N*-methyl-4-nitrobenzylamine Hydrochloride (**3f**·HCl).

From 2-hydroxy-4-nitrobenzaldehyde[10] (8.35 g, 50 mmol). The reaction was carried out in a similar way as in case of **3d**·**HCl**. Yield 2.7 g (25%), m.p. 243 °C (dec.). ^{1}H NMR (D_2O): 7.58 d, 1 H, J = 1.7 (H-3); 7.56 dd, 1 H, ^3J = 8.0 (H-5); 7.21d, 1 H, J = 8.0 (H-6); 4.01 s, 2 H (CH_2); 2.49 s, 3 H (CH_3).

Kinetic Measurements

The measurements of rate constants were carried out spectrophotometrically with a Specord M40, Carl Zeiss Jena apparatus. Chromatographic checking was performed using HPLC–Escom apparatus on column SGC C18 with 60% aqueous methanol at λ = 254 nm.

Chromatographic Method *D*

The 1 M solutions of carbamates **2a**–**2d** and **2f**–**2i** and 1,4-dichlorobenzene (internal standard) in dry dioxane in microampoules were heated in an oil bath at constant temperature in the range 110–180 °C. The ampoules were cooled at regular time periods, the contents diluted to 10^{-2} M using methanol and then injected to HPLC chromatograph. Rate constants k_c (s^{-1}) were calulated from the decrease of concentration of the starting carbamates **2**.

Spectrophotometric Method *E*

The $1 \cdot 10^{-2}$ M solutions of 4-nitrocarbamates **2e** and **2j**–**2n** in dry dioxane in microampoules were termostatted in an oil bath at 110 °C. Ampoules were cooled in regular time periods and their contents diluted to $5 \cdot 10^{-5}$ M solution by addition of aqueous acetate buffer (pH 5.65). 4-Nitrocarbamates **2e** and **2j** were also measured in toluene and were diluted to $5 \cdot 10^{-5}$ M solution by addition of methanol. For evaluation of the rate constants k_c, the absorbances of these solutions were measured in 1 cm cells at 280 nm (λ_{max} of 4-nitrophenol) and 350 nm, where the spectral differences of products and starting carbamates were maximal.

RESULTS AND DISCUSSION

Rate constants of cyclization k_c (s^{-1}) of carbamates **2** were measured in dioxane. 4-Nitrocarbamates **2e**, **2j**–**2n** formed products which were spectrally well distinguished from the starting carbamates using method *E*. Spectral differences of other carbamates and their products of cyclization were small and therefore it was necessary to insert chromatographical separation by method *D*. Cyclization of some carbamates, which proceed at temperature 110 °C very slowly, were carried out at higher temperatures. The obtained velocity constants k_c were recalculated to this temperature using the Arrhenius equation. A good agreement between the exptrapolated and measured value was verified for compound **2g** (Table I). Reactions were first order with respect to substrate concentration. For carbamates **2a**–**2e** (R^3 = H) and **2f**–**2j** (R^3 = Me) where there was a change of the substituent in the phenoxide leaving group (R^1 = R^2 = H), electron-withdrawing substituents increased the reaction rate, and the kinetics of cyclization were measured at 110–180 °C. At the highest temperatures there was decomposition of the product **1** (up to 7%).

The influence of substituents R^1 and R^2 in the aminomethylphenol nucleus was examined in case of 4-nitrophenyl derivatives **2j**–**2n**. In contrast

to the substituents on the leaving phenoxy group, the influence of substituents R^1 and R^2 on the rate of cyclization was small and all the measurements could be carried out at the same temperature 110 °C (Table I). To determine the effect of the substituents at the leaving phenoxy group the values of k_c measured at higher temperatures were extrapolated to 110 °C. The dependence of log k_c on T^{-1} was similar for all substituents $(-5.3 \pm 0.3) \cdot 10^{-3}$ K^{-1}, *i.e.* $\Delta H^{\neq}$ values are the same and the effect of the substituents is predominantly determined by the entropy of activation.

TABLE I
Rate constants k_c (s^{-1})[a] of cyclization of carbamates **2** to oxazines **1** in dioxane solution

Compound	$10^5 \cdot k_c$	*T*, °C	Method	Compound	$10^5 \cdot k_c$	*T*, °C	Method
2a	89.1	180	D	**2g**	129	150	–
	26.3	160	D		37.1	130	D
	0.67[d]	110	–		8.84	110	D
2b	87.1	150	D		8.9[d]	110	–
	30.2	130	D	**2h**	115	160	D
	5.4[d]	110	–		30.9	140	D
2c	138	170	D		3.8[d]	110	–
	36.3	150	D	**2i**	38.0	110	D
	2.1[d]	110	–	**2j**	955	110	E
2d	20.9	110	D		46.8[b]	110	E
2e	589	110	E		234[b,c]	110	E
	295[b]	110	E		295[b,c]	110	E
	571[b,c]	110	E		389[b]	110	E
	536[b]	110	E	**2k**	708	110	E
	567[b]	110	E	**2l**	617	110	E
2f	151	180	D	**2m**	794	110	E
	42.7	160	D	**2n**	891	110	E
	1.4[d]	110	D				

[a] Reported rate constants are the means of several determinations and are correct to ±5% in dioxane and about ±10% in toluene. [b] In toluene solution. [c] With 1 equivalent of triethylamine. [d] Extrapolated value. [e] With 2 equivalents of triethylamine. [f] With 4 equivalents of triethylamine.

The slope of log k_c on σ^0 constants (Fig. 1) has the value $\rho = 2.50 \pm 0.15$ and 2.40 ± 0.15 for N-H and N-Me derivatives (the k_c values for 4-nitro derivatives were not used for calculation of ρ constants), respectively, but the cyclization rate of the *N*-methyl derivatives is almost twice as high. On the basis of the kinetic experiments a one-hour reflux of 4-nitrophenyl carbamates in dioxane was found to be the most suitable procedure for the preparation of the substituted 4*H*-1,3-benzoxazin-2(3*H*)-ones **1**. The amount of unreacted carbamate was in all cases less than 1%. When the carbamate formed by the reaction of substituted aminomethylphenols with 4-nitrophenyl formate was isolated from the reaction mixture (procedure *A*) the mean yield, based on aminomethylphenol, was 62% and by the phosgene method (procedure *B*) 68%. When the preparation of the product was carried out without isolation of carbamate (procedure *C*), the yield was almost quantitative. The substituents in the leaving phenoxy group effect the rate of cyclization considerably ($\rho = 2.45$) this means that there is a substantial splitting of the C–O bond in the transition state. However the substituents in the second aryl nucleus have little effect on the rate of cyclization. This may be caused by the fact that the new C–O bond is formed only to a small extent or that there is a simultaneous formation of the O–C and splitting of the O–H bonds and the effect of substituents on both processes compensate: electron-withdrawing substituents make the formation of the O–C bond difficult, but they facilitate the splitting of the O–H bond.

If the cyclization proceeds by this mechanism, then the presence of triethylamine, which is more than 10-orders of magnitude a stronger base than dioxane, will increase the rate of cyclization. There was actually no catalytic effect of added triethylamine which means that there is no sub-

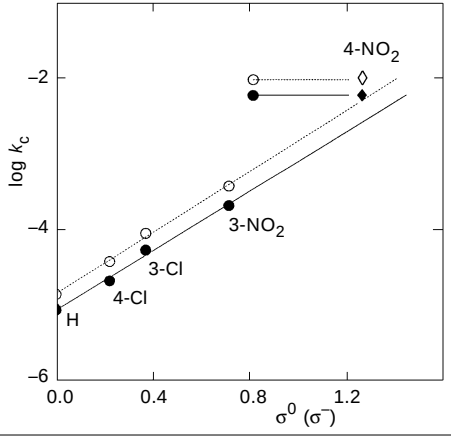


FIG. 1
Dependence of logarithms of cyclization rate constants of substituted phenyl *N*-(2-hydroxybenzyl)carbamates (●) and substituted phenyl *N*-(2-hydroxybenzyl)-*N*-methylcarbamates (○) on σ^0 constants in dioxane at 110 °C. For 4-nitrophenyl *N*-(2-hydroxybenzyl)carbamate (◆) and 4-nitrophenyl *N*-(2-hydroxybenzyl)-*N*-methylcarbamate (◊) on σ^- constant in dioxane at 110 °C

stantial splitting of the O–H bond in the activated complex. The transition state can be stabilized by formation of the hydrogen bond between basic solvent and the hydrogen of the O–H bonds, if it is stronger than in the substrate[11]. Hydrogen bond accepting ability of triethylamine (β = 0.71) is higher than that of dioxane[12] (β = 0.37), but its concentration is more than two orders of magnitude smaller hence it influences the rate of cyclization just slightly. Therefore we measured the kinetics of cyclization of 4-nitrophenyl carbamates **2e** and **2j** in toluene (β = 0.11) with and without triethylamine (Table I). The rate of cyclization without triethylamine in case of N-H derivative **2e** is *ca* twice and that of *N*-methyl derivatives **2j** *ca* twenty times lower than in dioxane. After adding triethylamine the values k_c gradually approach the values in dioxane. The increase of rate is faster in **2j** than in **2e**. In the presence of excess triethylamine all the substrate is obviously hydrogen-bonded to triethylamine so there is no more effect of further addition of triethylamine. This result is quite opposite to the kinetics of reaction of phenols with aryl isocyanates[13]. In toluene at 67 °C the rate of the intermolecular reaction increased linearly with the concentration of triethylamine (k = 256 ± 15) $l^2\ mol^{-2}\ s^{-1}$ and there was no reaction in the absence of triethylamine.

In conclusion, the cyclization of carbamates **2** in dioxane is a concerted reaction with breaking of the C–O bond being more advanced than formation of the O–C bond. The reaction is accelerated by H-bonding to a basic solvent, which is stronger in the transition state than in the substrate. The unusual structure of transition state may be due to a large number of reactive conformations characteristic of intramolecular reactions[14].

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